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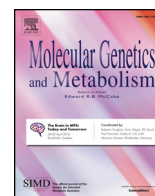
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Regular Article

Safety issues associated with dietary management in patients with hepatic glycogen storage disease



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ABSTRACT

Introduction: Hepatic glycogen storage diseases (GSDs) are a group of inherited disorders of carbohydrate metabolism for which dietary management is the cornerstone. Safety and acute complications associated with dietary management have been poorly documented. We hypothesized that safety issues and complications associated with dietary management are prevalent amongst patients with these ultra-rare disorders.

Methods: A questionnaire was developed consisting of 40 questions and was distributed via eight GSD patient organizations from multiple countries. Respondents were (caregivers of) patients with self-reported hepatic GSD.

Results: 249 GSD patients from 26 countries responded with a median age of 14.8 years (range: 0.5–66.1). Although management was considered safe by 71% of patients, 51% reported at least one acute complication associated with dietary management, with a total number of 425 reported complications.

Most frequently reported causes were: not waking up by an alarm clock ($n = 70$), forgetting a meal ($n = 57$) and infections ($n = 43$). Most frequently reported complications were: hypoglycemia ($n = 112$), hospital admissions ($n = 79$) and drowsiness ($n = 74$). Most complications occurred before the age of 12 years (82%; 637/774 total number of reported events) and during night time (63%; 340/536). Only 61% (152/249) of the GSD patients reported using a written emergency protocol.

Conclusions: Safety issues and complications associated with dietary management are prevalently reported by (caregivers of) 249 GSD patients. A discrepancy has been observed between the patient's perspective on safety of dietary management and occurrence of complications as a result of dietary management.

1. Introduction

Hepatic glycogen storage diseases (GSDs) are a group of inherited disorders of carbohydrate metabolism resulting from an enzyme or transporter deficiency in the glycogen synthesis or breakdown. Clinical presentation is characterized by fasting hypoglycemia, failure to thrive,

and hepatomegaly [1]. Dietary management is the cornerstone of therapy, which may include frequent feeds, continuous nocturnal gastric drip feeding (CNGDF) and/or uncooked cornstarch (UCCS). The introduction of dietary management has changed the prognosis of patients with several subtypes of GSDs from fatal into manageable diseases [2–5]. The general purpose/aim of dietary management in GSD

Abbreviations: ABGLICO, Associação Brasileira de Glicogenose; AGSD, Association for Glycogen Storage Disease; CGM, Continuous Glucose Monitoring; CNGDF, Continuous nocturnal gastric drip feeding; DM, Diabetes Mellitus; GSD, Glycogen Storage Disease; METc, Medical Ethical Committee (*translated*); n, number; N.R., Not responded; OMIM, Online Mendelian Inheritance in Man; PREMs, Patient Reported Experience Measures; PROMs, Patient Reported Outcome Measures; SHG, Glykogenose, Selbsthilfegruppe Glykogenose Deutschland e.V.; SAGSD, Scandinavian Association for Glycogen Storage Disease; VKS, Volwassen Kinderen en Stofwisselingsziekten; UCCS, Uncooked cornstarch; WMO, Medical Research Involving Human Subjects Act (*translated*)

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patients is to maintain normoglycemia, preventing secondary metabolic derangement and development of long-term complications, such as hepatocellular adenomas/carcinomas, (cardio) myopathy, renal failure and osteoporosis [6].

Despite improved dietary management for GSD patients, case reports have described fatal outcomes after technical and/or personal failures. Fernandes et al. has emphasized the necessity of a safety device in case of inadvertent placement of nasogastric tubes [3]. Both the European and American guidelines have acknowledged the importance of safety precautions, such as bed-wetting devices (to detect formula leakage), feeding pump alarms, tape, adapters, connectors and emergency protocols [6–8]. However, these previous studies have not been designed to systematically investigate dietary management associated safety issues.

Based on our experiences in our doctor's offices, we have hypothesized that safety issues and acute complications associated with dietary management are underreported and relatively common amongst GSD-patients. This information provides an extra dimension to discussions on reimbursement of medical devices and nursing support at home for (caregivers of) GSD-patients. Therefore, we aimed to assess the prevalence and the potential consequences of dietary complications and technical failures in patients with hepatic GSD. A questionnaire was developed and distributed with the support of eight international GSD patient organizations.

2. Methods

The Medical Ethical Committee (METc) of the University Medical Center Groningen stated that the Medical Research Involving Human Subjects Act (WMO) did not apply to this project and that an official review and approval of this study was not required (METc 2015/522).

2.1. Patients

Respondents were (caregivers of) patients with self-reported hepatic GSD. We excluded multiple entries by the same responder. GSD patients above the age of twelve years were invited to answer the questionnaire together with the caretaker/parent. Caretakers and/or parents were requested to fill in the questionnaire for patients below the age of twelve.

2.2. Questionnaire development

A focus group was composed consisting of health care providers, patients and carers, representing international patient organizations to draft, translate and distribute a SurveyMonkey® web-based questionnaire. The group included authors of this manuscript and the persons mentioned in the acknowledgements section. The questionnaire consisted of 40 questions on five pages in three distinctive segments: personal information, dietary management and complications (see supplementary material for the English version).

2.3. Questionnaire distribution

The final English version was translated by native speakers and distributed in the following languages: Dutch, English, French, German, Portuguese, and Spanish. Comments were translated via reverse translation. The questionnaire was distributed through social media by the following eight patient organizations: Association for Glycogen Storage Disease (AGSD, USA), Association for Glycogen Storage Disease – UK (AGSD-UK), Canadian Association for Glycogen Storage Disease (Canada), Glucolatino (Latin America), Associação Brasileira de Glicogenose (ABGLICO, Brazil), Selbsthilfegruppe Glykogenose Deutschland e.V. (SHG Glykogenose, Germany), Scandinavian Association for Glycogen Storage Disease (SAGSD, Scandinavia) and Volwassen Kinderen en Stofwisselingsziekten (VKS, The Netherlands).

The questionnaire was distributed on 15-03-2016 and closed on 25-07-2016, with a reminder sent on 10-07-2016.

2.4. Data analysis

In data analysis, acute complications were defined as either drowsiness and/or hypoglycemia. Severe complications were defined as those conditions, that would correspond with the definition of serious adverse events [9], including hospital admission, intensive care unit admission, seizures/epilepsy, coma and/or death.

2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v23.0 (Armonk, NY: IBM Corp.) and Microsoft Excel v.14.0.4734.1000 for Windows (Microsoft Corp., Redmond, WA, USA). Based on the sample size, the Kolmogorov-Smirnov test was used to test for normality. Since the data was not normally distributed, non-parametric tests were performed to examine differences between groups. For differences between groups, the Chi-Square test or Kruskal-Wallis test was performed, where appropriate. Differences were considered statistically significant at $p < 0.05$.

3. Results

In total 249 GSD patients from 26 countries responded, whose general characteristics are presented in Table 1. Mean age was 14.8 years (range: 0.5–66.1), 64% (159/249; 1 non-responders) of the patients were diagnosed before one year of age. Although management was considered safe by 71% (178/249) of patients, 52% ($n = 129$) reported at least one acute complication associated with dietary management. A total number of 425 complications was reported, including 364 severe complications. In Table 2, the complications and safety issues associated with dietary treatment are stratified by GSD subtype.

Table 3 presents the frequency of reported complications associated with the dietary management on a monthly basis (referring to question 26). Most frequently reported causes were: not waking up by an alarm clock ($n = 70$), forgetting a meal ($n = 57$) and infections ($n = 43$). In question 30, of the 129 patients reporting complications, most frequently reported were: hypoglycemia ($n = 112$), hospital admissions ($n = 79$) and drowsiness ($n = 74$). Less frequent complications were: ambulance called ($n = 57$), seizures/epilepsy ($n = 47$), intensive care unit admissions ($n = 39$) and coma ($n = 17$). In Question 31, the patients were asked to report the complications and the corresponding age at which the complications occurred. Most complications occurred before the age of 12 years (82%; 637/774 total number of reported events) and during night time (63%; 340/536). Fig. 1 shows the different age groups and their corresponding number and type of complications.

Only 61% (152/249) of the GSD patients reported using a written emergency protocol during intercurrent illness. Interestingly, patients with an emergency protocol had statistically more complications than patients without an emergency protocol (chi-square; $p < 0.001$). In this study, 17% of the patients did not have a glucose meter and an additional 14% of the patients did not use it. Of patients, 47% actively set an alarm and 5% reported using a bed wetting device to detect detached continuous feeds.

In Question 33, the patients were asked 'What was consequence of the severest complication?'. In total, 30% (43/142 total number of reported events) were managed at home, 46% required hospitalization, whereas intensive care unit admission and resuscitation were required in 18% and 5%, respectively.

Table 4 displays qualitative comments of (caregivers/parents of) GSD patients, illustrating the burden of the disease.

Table 1
Characteristics of (caregivers representing) GSD patients (referring to questions 2, 4 and 5).

GSD Type	Type 0	Type Ia	Type Ib	Type IIIa	Type IIIb	Type IV	Type VI	Type IX	Type XI	Unknown	N.R.	Total
n	3/249 (1%)	134/249 (54%)	39/249 (16%)	17/249 (7%)	5/249 (2%)	1/249 (0,4%)	3/249 (1%)	23/249 (9%)	2/249 (0,8%)	17/249 (7%)	5/249 (2%)	249
Male %	33%	44%	47%	47%	20%	100%	33%	63%	50%	68%		
Country of Origin												226 ^c
The Netherlands	–	3	–	3	–	–	–	3	1	–		10 (4%)
Germany	–	39	14	1	–	–	–	2	–	–		56 (22%)
Sweden	–	–	2	–	–	–	–	–	–	–		2 (1%)
Finland	–	–	–	2	–	–	–	–	–	–		2 (1%)
Brazil	–	31	8	3	1	–	–	1	–	8	2	54 (22%)
UK	–	–	–	1	1	–	1	–	–	–	1	4 (2%)
USA	3	32	6	3	–	–	1	10	1	3		59 (24%)
Norway	–	–	–	2	1	–	1	2	–	–		6 (2%)
Denmark	–	7	–	–	–	–	–	–	–	1		8 (3%)
Canada	–	8	7	–	2	1	–	4	–	–		22 (9%)
Other ^a	–	12	2	2	–	–	–	1	–	4		21 (8%)
N.R.	–	2	–	–	–	–	–	–	–	1	2	5 (2%)

N.R. is defined as Not Responded and indicates responders who did not answer the question. Unknown indicates responders who answered they did not know the GSD type. a = Patients were asked to choose their country of origin out of the countries specified in the table options (n = 226). 8% of responders indicated to originate from the following 16 countries (n = 21): Algeria (1), Australia (1), Bahamas (1), Chile (1), Croatia (2), France (1), Greece (2), Guatemala (1), India (2), Mexico (1), Pakistan (2), Poland (1), Russia (1), Spain (2), Switzerland (1), Yemen (1).

4. Discussion

Following previous case reports [10, 11], this is the first study of patient reported outcomes on safety issues associated with dietary management in a large cohort of GSD patients.

The majority of the total number of reported complications (82%) manifested before the age of twelve. Within this age group most events have been reported by caregivers of patients between 1 and 4 years of age (45%) and 4–12 years of age (31%). Several factors may complicate hypoglycemia awareness in young GSD patients. Young children are limited in communication and may be more vulnerable for both infections and their relatively high endogenous glucose requirements, the latter may fluctuate due to unpredictability in physical activity. Besides limitations in communication in preverbal children, compared to adults, children more often present with behavioral differences during hypoglycemia [12, 13]. In GSD I patients, hypoglycemia awareness may be affected by suppression of neuroglycopenic symptoms and signs, by the brain using lactate as an alternative source of energy [14].

Most complications (63%) occurred at night resulting from human errors which theoretically are preventable (e.g. forgetting a meal, forgetting to switch on the pump, misplacement of a tube and problems associated with an alarm clock). This indicates a potential hazardous timeframe, illustrating the necessity of safety measures to guarantee safety of the patient at night. In addition, this study indicates that patients (and caregivers) may have a distorted safety perception and may therefore not be aware of the potential hazards of dietary management. Systematic check-ups by the caregiver/parent and increasing the availability of devices (such as alarming subcutaneous Continuous Glucose Monitors (CGM)) are important preventive measures to increase safety.

In line with previous reports [2, 10], the comments of the respondents in this study highlight the burden associated with the intense dietary management (Table 4). It has been described that GSD patients report a lower quality of life than healthy controls [15]. Additionally, a significant severity of distress amongst the caretaking parents is reported. GSD patients require a time-intensive dietary management with continuous vigilance, as fasting tolerance is severely affected and blood glucose concentrations drop within minutes. The constant fear of hypoglycemia can be stressful for patients and their families and the resulting exhaustion brings an increased risk of developing complications [5]. Therefore, safety precautions with the aim to prevent hypoglycemia and increase awareness of hypoglycemic symptoms could potentially contribute in reducing disease burden for both the patient and

caregiver.

Besides alarm clocks, bed wetting devices and hand devices to monitor blood glucose concentrations, there is increasing experience with the use of subcutaneous CGM-meters in GSD patients [16–19], such as recent introduction of the Freestyle Libre [20]. The newest generation of CGM devices support real-time following and alarming to caregivers, which could be beneficial in preventing and detecting hypoglycemia. Moreover, the technology would increase the opportunities of families to immediately check the glucose concentrations at any given moment in time. This provides the possibility to detect hazardous moments such as nocturnal- and severe asymptomatic hypoglycemia and hypoglycemia in preverbal children, implementing an additional layer of safety and creates opportunities to recognize fluctuations for optimizing regimens. These advantages should obviously be balanced against the potential disadvantages, such as medicalization, technical failures by these devices, measurements of non-severe (asymptomatic) hypoglycemia and possible interference of organic compounds (e.g. uric acid and lactate).

Of the patients included in this study, 61% used an emergency protocol. Interestingly, patients with an emergency protocol had significantly more complications. Likely, respondents reflect the well-informed patient community, who are better prepared with emergency protocols. However, in some situations in more severely affected patients, experienced complications may have preceded health care professionals to provide an emergency protocol. Emergency protocols are in theory a beneficial safety measure, as the immediate correct treatment may be delayed by health care providers due to the unfamiliarity of these complex and rare diseases. Longitudinal data on the effectiveness of emergency protocols is warranted.

There is a gap between disease guidelines for cohorts of patients and individual patient care plans. Similar to GSD patients, patients with Diabetes Mellitus (DM) are also vulnerable to nocturnal hypoglycemia. Inadequate amount of hepatic glycogen in insulin-deficient diabetes patient increases the risk of nocturnal hypoglycemia [21]. However, in contrast to GSD patients, DM patients have (age-specific) guidelines and recommendations providing information regarding the safety, administration, pitfalls of their management [22, 23]. Recommendations for optimal metabolic control by dietary management of GSD I and GSD III patients are available in guidelines [6, 7, 24, 25]. However, these guidelines describe large cohorts and do not focus on individual patients. Additionally, the safety outcomes of dietary management and prevention of acute complications are neither discussed nor mentioned, and is overall rarely found in literature. A recent study of our center

Table 2
Complications and safety issues associated with dietary management stratified by GSD type.

GSD Type	Type 0	Type 1a	Type 1b	Type 1Ila	Type 1Ilb	Type IV	Type VI	Type IX	Type XI	Unknown	N.R.	Total
Number of patients (n)	3/249 (1%)	134/249 (54%)	39/249 (16%)	17/249 (7%)	5/249 (2%)	1/249 (0.4%)	3/249 (1%)	23/249 (9%)	2/249 (0.8%)	17/249 (7%)	5/249 (2%)	249
Patients with at least one reported complication	0/3 (0%)	69/134 (51%)	27/39 (69%)	9/17 (53%)	4/5 (80%)	0/1 (0%)	1/3 (33%)	11/23 (48%)	0/2 (0%)	6/17 (35%)	2/5 (20%)	129/249 (52%)
Drowsiness	0/3 (0%)	39/134 (29%)	13/39 (33%)	5/17 (29%)	2/5 (40%)	0/1 (0%)	1/3 (33%)	8/23 (35%)	0/2 (0%)	5/17 (29%)		73/249 (29%)
Hypoglycemia	0/3 (0%)	56/134 (42%)	24/39 (62%)	8/17 (47%)	4/5 (80%)	0/1 (0%)	1/3 (33%)	11/23 (48%)	0/2 (0%)	7/17 (41%)		111/249 (45%)
Coma	0/3 (0%)	10/134 (7%)	3/39 (8%)	2/17 (12%)	0/5 (0%)	0/1 (0%)	0/3 (0%)	2/23 (9%)	0/2 (0%)	0/17 (0%)		17/249 (7%)
Seizures/Epilepsy	0/3 (0%)	19/134 (14%)	14/39 (36%)	2/17 (12%)	1/5 (20%)	0/1 (0%)	0/3 (0%)	6/23 (26%)	0/2 (0%)	3/17 (18%)		45/249 (18%)
Called ambulance	0/3 (0%)	33/134 (25%)	15/39 (38%)	3/17 (18%)	1/5 (20%)	0/1 (0%)	0/3 (0%)	3/23 (13%)	0/2 (0%)	1/17 (6%)		56/249 (22%)
Hospital admission	0/3 (0%)	42/134 (31%)	19/39 (49%)	4/17 (24%)	2/5 (40%)	0/1 (0%)	0/3 (0%)	7/23 (30%)	0/2 (0%)	3/17 (18%)		77/249 (31%)
Intensive Care Unit admission	0/3 (0%)	24/134 (18%)	8/39 (21%)	3/17 (18%)	1/5 (20%)	0/1 (0%)	0/3 (0%)	2/23 (9%)	0/2 (0%)	1/17 (6%)		39/249 (16%)

N.R. is defined as Not Responded and indicates responders who did not answer the question. Unknown indicates responders who answered they did not know the GSD type.

Table 3
Frequencies of complications associated with the dietary management that occur on a monthly base (referring to question 26).

	Not waking up by alarm clock	Forgetting a meal	Pump Failure	Gastric Tube dislocation	Gastric Tube occlusion	Nasogastric tube dislocation	Nasogastric tube occlusion	Connector leakage	Electricity failure	Infections	Out of stock problems	Wrong calculations in prescription	Preparations Problems ^a
Never	30	36	34	43	39	42	42	33	51	30	48	49	48
1 ×	28	22	17	10	10	6	2	23	8	18	7	9	11
2 ×	17	13	13	3	5	4	5	8	–	7	2	4	4
3–5 ×	18	10	6	2	2	2	1	5	5	10	1	1	3
6–10 ×	4	6	1	–	–	1	2	4	4	5	1	3	–
> 10 ×	3	6	1	–	2	1	–	2	–	3	2	3	5
Total	54% (70/129)	44% (57/129)	29% (38/129)	12% (15/129)	15% (19/129)	11% (14/129)	8% (10/129)	33% (42/129)	13% (17/129)	33% (43/129)	10% (13/129)	16% (20/129)	18% (23/129)

Responses from 129 patients who answered 'yes' to question 25 (i.e. 'Have you ever had any complications associated with the previous and/or current dietary management?'). N.R. is defined as Not Responded and indicates responders who did not answer the question.

^a Preparations problems; i.e. measuring of feeding.

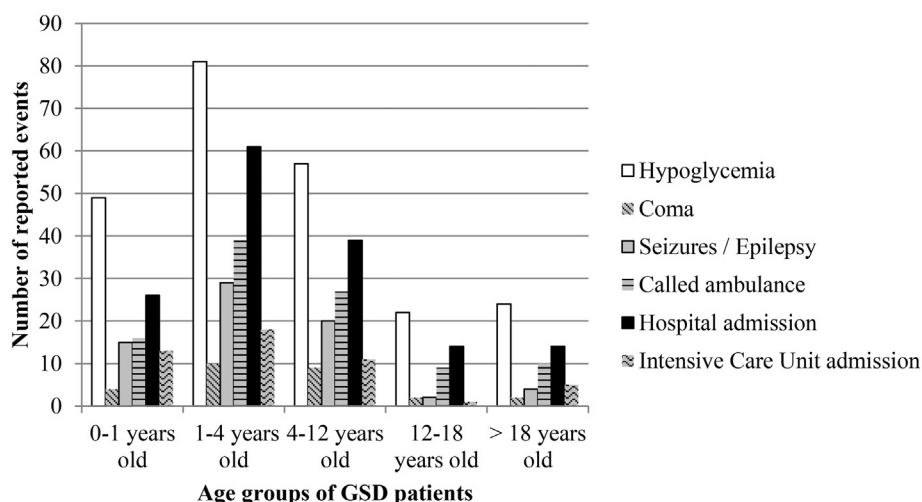


Fig. 1. Different patient age groups and their corresponding number and type of reported complications. Results refer to questions 25 and 31 from the original questionnaire.

Table 4

Selection of additional patients' comments. Results refers to the comment section and the end of the original questionnaire.

"We (parents) set the schedule and parameters but care is provided by in home nurses approximately 90% of all nights. Without the nursing assistance, this feeding program would not be safe for our son."

"Waking up in middle of every night is extremely hard when we are working 2 jobs to support and provide for child. There is a fear of not waking up. 15 alarms are set every night."

"GSD is a very complicated disorder which can become critical within short time. We have been VERY cautious and have been able to catch symptoms before they progress to major complications."

focused on heterogeneity between GSD Ia patients. This study states that there is no clear definition of good metabolic control and emphasized the need for an individualized approach to dietary management for GSD Ia patients [26]. Along with the complexity of GSD, the paper by Shah and O'Dell, and the published commentary of Derks et al. highlights the difficulties in dietary management of GSD patients and emphasizes the lack of information of long-term follow-up data [27, 28]. Therefore, acquiring disease specific patient derived big data by developing a registry could be beneficial in terms of safety- and treatment measures for both the medical healthcare professional as for the patient. These developments will be important stepping stones in patient-centered health care for which several legal and technical challenges need to be bridged.

Some methodological issues of our patient centered study need to be addressed. First, our questionnaire was designed to make an inventory of patient reported outcomes on safety in general, rather than to compare the safety situations between patients of different GSD subtypes or differences between dietary managements. Unfortunately, the anonymous data provided by patients could not be double checked by the treatment center of the patient, hence the genetic diagnosis could not be confirmed. We cannot completely exclude that a subset of the respondents who reported an unknown type of GSD may suffer from an alternative diagnosis. Our data on safety related to complex dietary treatment, however, presents a unique perspective from the patient's point of view and is further supported by the high number of responders. Secondly, this study has been impacted by ascertainment bias, towards relatively well-informed individuals, who engage with patient organizations and/or social media. Response rate could not be determined as the distribution did not allow to indicate the denominator from which the sample size was drawn. Therefore, one can only speculate how the distribution of the questionnaire has affected the results of this study. Respondents may have been overrepresented by

severe cases, due to unreachability or unresponsiveness of milder patients. On the contrary, responses about deceased GSD-patients may have been underrepresented too.

Nevertheless, this is the first ever study of its kind on safety issues related to dietary management of GSD patients and it is of interest to health care providers, patients, caregivers and health care policy makers who shape future health care. Dietary management for hepatic GSD-patients is complex for many reasons, including the complexity of the disease and fast variations in glucose homeostasis, non-compliance with glucose monitoring and problems of reimbursement of medical devices (like traditional blood glucose/ketone monitors, continuous glucose monitors) and home care. The questionnaire could be applied prospectively in collaborating centers to provide a denominator and more comprehensive data collection, ideally in web-based applications connected with hospital based electronic patient files [29].

As some complications would fulfill the definition of serious adverse events, safety assessment for medically prescribed diets in patients with inherited metabolic diseases deserve the same level of awareness and safety assessment compared to (the prescription of) regular medicines.

We report a high prevalence of safety issues and complications associated with dietary treatment in hepatic GSD-patients, especially amongst the youngest patients and at night. This information provides an important dimension in discussions on reimbursement of medical devices and nursing support at home for (caregivers of) GSD-patients. Ideally, safety outcomes should be integrated in communications on patient reported outcome measures and patient reported experience measures [30]. The application of modified FAIR (findability, accessibility, interoperability, and reusability) guiding principles is beyond scientific data management but will be a crucial precondition for health care data management, especially for patients with ultra-rare diseases.

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Conflict of interest

None.

Contribution of individual authors

Thomas A.H. Steunenberg was involved in the design of the study and questionnaire, acquisition, analysis and interpretation of the data, wrote the first draft of the manuscript, revised the manuscript critically for intellectual content and gave final approval of the version to be submitted.

Fabian Peeks was involved in the design of the study and questionnaire, acquisition, analysis and interpretation of the data, drafted the manuscript, revised the manuscript critically for intellectual content and gave final approval of the version to be submitted.

Irene J. Hoogveen critically reviewed the questionnaire, was involved in the analysis and interpretation of the data, drafted the manuscript, revised the manuscript critically for intellectual content and gave final approval of the version to be submitted.

John J. Mitchell is responsible for the care of GSD patients at Montreal Children's Hospital and was involved in the drafting of the manuscript, revised the manuscript for intellectual content, distributing the questionnaire and gave final approval of the version to be submitted.

Helen Mundy is a consultant in pediatric inherited metabolic medicine in Evelina London Children's Hospital and was involved in the drafting of the manuscript, revised the manuscript for intellectual content, distributing the questionnaire and gave final approval of the version to be submitted.

Foekje de Boer is a dietician in pediatric metabolic diseases in the UMCG and was involved in the drafting of the manuscript, revised the manuscript for intellectual content and gave final approval of the version to be submitted.

Charlotte M.A. Lubout is a pediatrician metabolic diseases and was involved in the drafting of the questionnaire and manuscript, revised the manuscript for intellectual content and gave final approval of the version to be submitted.

Carolina F. de Souza is a medical geneticist in Porto Alegre clinical hospital and was involved in the drafting of the manuscript, revised the manuscript for intellectual content, distributing the questionnaire and gave final approval of the version to be submitted.

David A. Weinstein was previously responsible for the care of GSD patients at the University of Florida and is at present responsible for GSD patients at Connecticut Children's Medical Center. He was involved in the drafting of the manuscript, revised the manuscript for intellectual content and gave final approval of the version to be submitted.

Terry G.J. Derks is responsible for the care of GSD patients in the UMCG, initiated and designed the study and questionnaire, analysis and interpretation of the data, drafted the manuscript, revised it critically for important intellectual content and gave final approval of the version to be submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgme.2018.07.004>.

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